AstraZeneca

COPY 1

Date: FEB 13 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 01D-0489
Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Dear Sir or Madam:

Reference is made to the November 20, 2001 *Federal Register* Notice (Docket No. 01D-0489) announcing the availability of Draft Guidance for Clinical Trial Sponsors entitled, "***The Establishment and Operation of Clinical Trial Data Monitoring Committees***".

AstraZeneca Pharmaceuticals LP (AstraZeneca) has reviewed this draft guidance and our comments are outlined in the attached document. AstraZeneca hopes that the Agency finds this information useful in clarifying and adding to the pending final guidance document.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Thank you for your consideration.

Please direct any questions or requests for additional information to me.

Sincerely,

Mark Scott, Ph.D.
Executive Director
Regulatory Affairs
(302) 886-8495
(302) 886-2282 (fax)

MS/kc

Enclosure

01D-0489

C 11

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224,
Notices, Pages 58151 – 58153

General Comments:

- Comment 1: The guidance document is well written and thorough. It is clear that a great deal of work went into it, and the authors are to be commended. The document will be very useful and important to both pharmaceutical and government sponsors of clinical trials. The principal behind Data Monitoring Committees (DMCs) is a valid and good one for patient protection, as well as to provide a reality check to the sponsor regarding trials that may need to be reevaluated. There might be some resistance on the part of sponsors to use them though unless required.

- Comment 2: The guidance document focusses on DMC for individual trials; it may be useful to add in the document that there may also be value to consider a DMC across an entire clinical trial program.

- Comment 3: It would be very beneficial for the guidance to address issues posed by open-label or single-blind studies. In many cases oncology studies are not double-blind, and since they usually have a mortality endpoint it is especially important for sponsors to understand how best to approach such studies with respect to interim analyses and DMCs.

- Comment 4: As the guidance appropriately indicates, there are instances in earlier phases of research (e.g. Phase 2) where an internal group can comprise the DMC. We suggest that the guidance state more explicitly that the FDA will not discount the data from such a study, potentially providing data that are supportive of the label indication, when the sponsor follows a well-defined and documented process to ensure the clinical study team remains blinded.

- Comment 5: Although an independent DMC has the advantage of a perception of lack of bias, it has an important disadvantage of replacing full-time sponsor experts with part-time non-sponsor individuals. External independent members would be chosen from the class of experts in the disease, or experts in statistics. However, they only spend a day or two evaluating and interpreting each interim analysis. We suggest that this be acknowledged in the guidance. Dr. Robert Temple presented the concept of what he referred to as "DMC Type II" at the FDA workshop for this draft guidance held on November 27, 2001. For this type of DMC, Dr. Temple espoused that the need for independence is not as great in the

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224,
Notices, Pages 58151 – 58153

situation where safety alone is being analyzed across a series of clinical trials. We suggest that this be further described in the guidance document.

- Comment 6: Although, well written, the guidance document fails to elaborate on agreements between sponsor and the DMC as to data to be supplied to the DMC. In addition, there are no specific guidelines on suggested management of disagreement(s) between the sponsor and the DMC.

- Comment 7: Interactions between DMC and Steering Committee – a brief statement regarding when it might be helpful and a statement describing the differences in responsibilities for each may be useful.

- Comment 8: Some of the terminology, within the document, needs clarification and/or definition. In particular, "Steering Committee" should be defined in the guidance. We suggest something like "DMC Steering Committee", defined as the group to whom the DMC makes their recommendation (may or may not include sponsor personnel, for example). And, where the guidance refers to "SOPs" (section 4.3), it should instead refer to this document as a DMC Charter. That is, a charter needs to be created uniquely for each DMC, but each sponsor should have an SOP that describes the process relating to DMCs.

- Comment 9: Although the DMC can only recommend to terminate a trial, what would be the legal/regulatory implications to the sponsor of not following that recommendation? Would FDA consultation and approval not to follow the recommendation be required?

- Comment 10: Although the guidance is intended to not limit sponsors to a specific process, the FDA should acknowledge that even the word "should" will be interpreted as "must" by sponsors of clinical trials. One solution is to soften the message by providing more balanced advantages and disadvantages to the suggestions presented in the guidance.

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224,
Notices, Pages 58151 – 58153

General Comments (Biostatistics):

- Comment 1: While the document recognizes that the statistician providing the data for the DMC should have in-depth knowledge of the study, the mandate that the statistician should be external to the clinical trial ignores the logistical difficulty of how to accomplish this, especially in situations where a sponsor has limited statistician resource available. The recommendation to hire a statistician from a CRO for this purpose does not resolve the conflict of interest problem, since this person would then become an employee of the sponsor. Also, if an external Data Coordination Center is used, the Center has a financial incentive to discourage the DMC from stopping the study. The document also does not take into account that even if the clinical team statistician just prepares the analysis program, and another person performs it, DMCs frequently need in-depth explanations of the analysis, or request additional analyses that would require the expertise of the original author, so the team statistician would still need to be involved.

- Comment 2: The guidance strongly recommends that the statistician who conducts the interim analysis and presents the data to the DMC be external to the sponsor in all cases where the study may be used as a registration study. Although there will be cases where this may be the most appropriate approach (e.g. mortality studies), the majority of clinical studies need not and should not go to this extreme. The analyzing statistician can come from within the sponsor and still be isolated from the study team, completely maintaining the blind for sponsor personnel who are involved in the study. There are several distinct advantages to having the analyzing statistician come from the sponsor including:

    a. Statisticians within the sponsor have access to proprietary standard analysis systems which lead to greater accuracy, consistency, and efficiency
    b. Statistical and disease-specific expertise is usually greater within the sponsor, including greater knowledge of the specific protocol and previous clinical data
    c. There is the potential for financial conflict of interest with an external Data Analysis Group, as they are financially compensated for many weeks or months of work to conduct a single interim analysis.

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224,
Notices, Pages 58151 – 58153

- Comment 3: Since FDA does not have an Interim Analysis Guidance, Sections 4.3.2, 6.3 and 6.4 could be interpreted/used by FDA reviewers as the guidance for any interim analyses (Phase I - IV). To avoid the confusion, we suggest that the document clearly state that the IA process (e.g. the involvement of external statisticians) indicated in this document is intended to be used for studies with an external DMC only.

- Comment 4: A DMC recommendation to stop a mortality or serious morbidity study for positive efficacy is the penultimate of recommendations. It is critical in such situations, from a societal perspective, that the chance of the FDA or an advisory committee disagreeing with the DMC recommendation is very small. How to achieve this is discussed to some extent in Sections 4.4.1.1, 5.2, and 7.2.1. We first suggest that this important topic be combined into a single section. We further suggest expanding the discussion to provide additional ideas of what the DMC may need to consider before they recommend study termination. For example, important subgroups for the DMC to evaluate should be identified in the DMC charter. Finally, for such studies we recommend that the guidance strongly encourage FDA involvement in the protocol and charter development, in order to define aspects of what is required for approval (e.g. one study at two-sided alpha level of 0.05, a trend in an important subgroup, etc.).

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224,
Notices, Pages 58151 – 58153

General Comments (Drug Safety):

- Comment 1: The document essentially ignores the safety surveillance role of the sponsor's safety department, and provides no guidance on how this group should partner with the DMC in ensuring study subject safety. In our company's experience, the safety department frequently provides data to the DMC, since the safety database contains additional details about serious adverse events that are not contained in the clinical database (eg, information from hospital records that are not captured in the case report forms) but this is not recognized in the document.

- Comment 2: Perhaps another member of a Data Safety Monitoring Board could be a drug safety specialist who is neither involved with the sponsor or another firm.

- Comment 3: Perhaps it would be helpful if literature were being formally reviewed by the sponsor on safety issues regarding competitors or the same drug class, the target population or any significant new developments on an ongoing basis especially for long-term outcome studies. Any important articles could be forwarded to the DMC.

- Comment 4: It would also be useful for the DMC to receive data from other INDs involving the same drug or from the postmarketing database of a marketed product. Perhaps for marketed products, copies of the annual Periodic Safety Update Reports with exposure data. Also, in some cases, more than one DMC may be necessary.

- Comment 5: It may also be useful for the DMC to receive discussions regarding safety issues such as Safety, Evaluation and Review Meeting documents or responses to queries from World Wide Regulatory Affairs.

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comment
2	3	*Determining Need for a DMC*	This section briefly mentions large, relatively short-term trials (e.g. trials in gastric cancer, or recurrent head and neck cancer), however, the guidance document in general does not adequately address the problem of how to handle DMCs in short-term trials where it may be difficult to collect and analyze data before the trial has completed accrual.
2.1	3	*Risk to Trial Participants*	This section contains multiple points that are difficult to view clearly. Providing the points as a bulleted list would be a better option.
2.2	3	*Practicality of DMC Review*	This section does not adequately describe criteria or metrics to determine in advance for any given trial, that the DMC will have the capacity to collect, analyze, and interpret accumulating data in real time so that they can fulfill their mandate to monitor accumulating results and provide recommendations for early intervention.
3	4		Recommend the addition of a subsection which highlights the Sponsor's responsibility with regard to ongoing monitoring of safety within clinical trials and programs.
3.1	4	IRBs	As currently written, this section does not sufficiently distinguish the boundaries between DMC and IRB responsibilities. Our company's experience has been that IRB's are demanding a DMC-type level of data analysis with increasing frequency, even when a DMC is in place and sends out communications regularly. It is a concern that this guidance will encourage this type of behavior, even though IRB's do not always have members with sufficient expertise to interpret data correctly.
3.5	5	*Others with Monitoring Responsibilities*	The section neglects to mention the role of the sponsor's safety department, which certainly has safety monitoring responsibilities as well. Additionally, the safety department has a product-wide view of the safety of the product, rather than just the narrowly focused clinical trial subsection viewed by the DMC.

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
3.5	5	3rd sentence	The sponsor is responsible for **MONITORING AND** tracking these investigator reports (add bolded text)
3.5	5	Last sentence	**THE SPONSOR AND FDA**, in turn, is responsible for … (add bolded text)
4.1	5	*Committee Composition*	This section states that the DMC should contain "at least one biostatistician" and that is fine. One may even recommend to have at least two biostatisticians for large pivotal studies of mortality and the like, because very heavy responsibility lies on a single biostatstician in such studies when no one else in the committee is likely to understand the technicalities involved in the statistical considerations.
4.1	5	*Committee Composition*	Recommendations for membership should be more specific, in particular depending of the trial phase or trial size. The DMC should be nominated together by the sponsor and Steering Committee not **and/or**.
4.1	5	1st paragraph	Committee Composition: "A DMC that fails to note problems that should be addressed, or that makes recommendations that are unwarranted or whose consequences are inadequately considered, can undermine the safety of participants as well as the value of the trial." What measures should the sponsor use to safeguard against the above outcomes? Should the sponsor seek a second, independent interpretation and confirmation of the unblinded data reviewed by the DMC? Should there be a backup DMC or alternate members for this purpose with a pre-defined process?

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
4.2	7	1st paragraph	Confidentiality of Interim Data and Analyses: "... interim data and the results of interim analyses should generally not be accessible by anyone other than DMC members." This should be qualified to refer to unblinded interim data and results. Section 2.3 states the trial organizers can make changes to the trial from accumulating data within the trial such as overall event rates.
4.2.2	7	*Interim Reports to the DMC*	The data should be reviewed and broken down by treatment groups but blinded. If there appears to be a safety or efficacy issue, the blind can be broken to determine the risk/benefit ratio and make decisions. Even in open-label trials, reviewers should be blinded to treatment groups.
4.3	8	*Establishing SOP*	We also need to define the roles for each DMC member in the SOP.
4.3.2	11	*Statistical Methods* 1st paragraph	Statistical Methods: It is stated that a DMC is not obligated, due to other aspects of the interim data, to recommend termination of a trial if the prospective defined stopping boundary for positive results is crossed, even if the data on effectiveness if very strong. A similar statement is made in the first paragraph of 4.4.1.2 – Monitoring for Safety. This is not universally appropriate advice. If there is very strong evidence of effectiveness, and the criteria are met for termination, then the trial should stop. If there are major concurrent safety concerns, which are so extreme that they outweigh strong evidence of effectiveness, then the trial should also stop on the basis of safety.

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
4.3.2	12	Last paragraph Last sentence	The sentence states "Nevertheless, protection of Type I error is important even when there is a stated intention to stop early only for futility reasons since interim review of outcome data always raises the possibility that the DMC may find early results so persuasive that it would recommend early termination of the trial." We agree with this position for mortality or serious morbidity studies, where ethical reasons would dictate early stopping for strong positive efficacy results. However, in other studies, it often is not the case that the DMC can recommend stopping for positive efficacy; the interim may be conducted to test for futility, or to evaluate safety. Consequently, it is scientifically and statistically appropriate to not spend any alpha (i.e. not make any adjustment to the final nominal alpha level) in these cases. In fact, Section 4.4.1.5 of the guidance document essentially agrees with this position (and contradicts the previous quote from the guidance), where it states "Early termination for effectiveness is rarely appropriate in such studies."
4.4.1.2	12-13	*Monitoring for Safety*	This section should include a discussion of when it is appropriate to obtain a waiver for expedited reporting of study endpoints, and describe some appropriate strategies for collection and analysis of safety information (eg, mortality and morbidity endpoints) when a waiver is in effect.
4.4.1.2	13		Monitoring for Safety (Last paragraph): "The DMC should learn in a timely manner of any cases for which unblinding of treatment code at the clinical site or by the treating clinician is thought to be necessary to provide an appropriate intervention." There could be bias in detecting all cases of such unblinding in a trial for which the process for unblinding is not centrally authorized and controlled.

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
4.4.1.2			Outside of the sponsor obligations for AE reporting as currently regulated, the expectations/guidelines regarding reporting of IDMC findings or recommendations to the FDA are left too vague.
4.4.1.2	13	3rd paragraph 2nd sentence	… has the responsibility of reporting serious, unexpected **AND RELATED** adverse events in drugs (add bolded text)
4.4.1.3	14	*Monitoring Study Conduct*	Recruitment rate, effects of external data, etc. are often considered by steering committees rather than DMCs.
4.4.1.4	14-15	*Consideration of External Data*	While this section speaks to the impact of "release of results of a related study" (second sentence, first paragraph) it does not discuss how "real-time" incoming data (for example, expedited reports of adverse drug reactions from other clinical studies or non-investigational sources if the drug is marketed) could be shared in a meaningful way with the DMC.
4.4.1.4	14	3rd paragraph	It states "In many cases, access to the blinded data…" We believe you mean to say "unblinded" here, as this paragraph addresses how the DMC may be able to utilize external data along with their knowledge of the unblinded interim data from the current study.
4.4.3.1		*Making Recommendations*	Recommendations are frequently made to the steering committee rather than the sponsor. It is places such as here that it is important to consider the role and remit of steering committees.
4.4.3.1		*Making Recommendations*	It is very unclear about what happens in the event the DMC has a recommendation for a significant trial modification or termination with regard to how much discussion and/or data will be accessible to the sponsor. Secondly, a great deal of time is spent discussing those situations which might be pertinent for having a DMC but it is never stated who actually makes the decision about having a DMC. Is it assumed that it's the sponsor, however, would FDA have the right to suggest or direct it as well?

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
4.4.3.1	16	2nd paragraph	Making Recommendations: "The DMC should express its recommendations very clearly to the sponsor. … Recommendations for modification other than termination should be accompanied by the minimum amount of data required for the sponsor to make a reasoned decision about the recommendation and the rationale for such recommendations should be as clear and precise as possible." There needs to be a balance between the need to provide a very clear reason for the DMC's recommendation and the need to avoid providing unblinded interim results to the sponsor. Any recommendations are likely to be the result of an imbalance in safety or efficacy between the treatment arms. It needs to be recognized from the start that the DMC has been given the responsibility of making recommendations based on their own judgment and, to maintain the integrity of the trial, the DMC should not be unduly influenced. If there is reluctance to implement the DMC's recommendations, then what is the best course of action? For example, should the sponsor independently confirm the recommendation by bringing in designated alternate DMC members to review the unblinded data?
4.4.3.1	16	2nd paragraph	We suggest that the 2nd paragraph in Section 4.4.3.1 be expanded to provide more guidance about what should occur after the DMC makes their recommendations to the sponsor in order to continue to maintain the data integrity. This is especially critical when the DMC recommendation is to stop the study for positive results. Additionally, the guidance should emphasize the importance of the DMC recommendation being communicated to the Steering Committee in a timely fashion.

Draft Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

Docket Number: Docket No. 01D-0489
Federal Register: November 20, 2001, Volume 66, Number 224, Notices, Pages 58151 – 58153

Section	Page No.	Line No. or Paragraph No. (if applicable)	Comments
5.1	17	1st paragraph 2nd sentence	…prompt reporting to FDA of unexpected **RELATED** adverse events (add bolded text)
5.1			Outside of the sponsor obligations for AE reporting as currently regulated, the expectations/guidelines regarding reporting of IDMC findings or recommendations to the FDA are left too vague.
5.1	18		Safety Reporting (Last paragraph): "Sponsors should notify FDA and the responsible IRBs of any recommendations or requests made by a DMC to the sponsor that address safety of participants…" This should be conditional on whether the sponsor and/or Steering Committee concurs with the recommendations or they are feasible to implement.
5.2	18		Expedited Development: This states that there may be certain new therapies for which the FDA may need to interact with the DMC in an ongoing trial. This interaction should be restricted to sharing of information discussed in open sessions of DMC meetings.
6.4		*Conduct of the Interim Analyses*	Further discussion should be made to support the appointment of an external statistician to conduct an interim analysis.
6.6		*Use of Interim Data in Regulatory Submissions*	Section 6.6 warns that interim data should not be used in a submission. We suggest that submissions based on interim analyses while the study continues may be valid, so long as the protocol provides clear criteria for when a submission would occur.

ASTRA ZENECA PHARMACEUTICALS LP
US REGULATORY AFFAIRS
1800 CONCORD PIKE
PO BOX 6565
WILMINGTON, DE 19803-6565

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

1 LBS 1 OF 1

ASTRA ZENECA PHARMA
302 886-2806
1800 CONCORD PIKE
WILMINGTON DE 19803

SHIP
TO:

FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE
ROCKVILLE MD 20857

MD 207 9-06

UPS GROUND

TRACKING #:1Z X29 W25 03 0017 1091

BILLING: P/P

INV#:60621

ASC 05.00 J69X/164X 16.0A 01/ 002